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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,905	12/14/2001	Paul M. Ridker	B0801/7238 (ERG/KA)	7653

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/017,905	RIDKER ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,11,16,21,52,55,57,62-68 and 71-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,6,11,16,21,52,55,57,62-68 and 71-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 9/21/09, and IDS, filed 9/28/09, have been entered.

2. Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 are being acted upon.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Rodriguez-Moran et al. (1999) in view of Rohlfing et al. (2000) and Chapin et al. (1999).

As set forth previously, Rodriguez-Moran et al. teaches that elevated serum CRP levels have been found in type II diabetics and in diabetics with foot ulcers (see particularly page 211, column 2). The reference also teaches that elevated serum CRP levels are also found in noncontrolled type II diabetic patients. (see particularly Table 2).

Rodriguez-Moran et al. does not teach the characterizing a risk profile for developing diabetes in an apparently healthy individual nor evaluating the likelihood that an individual will benefit from treatment.

Rohlfing et al. teaches the use of a screening assay for undiagnosed diabetes and/or complications thereof (see particularly page 187 and CONCLUSIONS).

Chapin et al. teaches that even apparently healthy individuals who undergo regular physical examinations can suffer from undiagnosed diabetes and/or complications thereof (see particularly Table 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made measure serum CRP levels for uses such as characterizing a risk profile for developing diabetes in an apparently healthy individual or evaluating the likelihood that an individual will benefit from treatment given CRP's known association with type II diabetes, as taught by Rodriguez-Moran et al., given that it is well known to measure a known marker for the presence of, or predisposition to, diabetes, as taught by Rohlfing et al., even in apparently healthy individuals because even apparently health individuals can suffer from undiagnosed diabetes and/or complications thereof, as taught by Chapin et al. Note that the choice of any particular serum CRP concentration as

an indicator of disease comprises no more than routine optimization of the claimed method and falls well within the purview of the ordinarily skilled artisan.

Applicant's arguments, filed 5/09/08, have been fully considered but are not found persuasive. Applicant again makes a curious argument that the teachings of Rodriguez-Moran et al. cannot be used to render obvious the predictive value of CRP levels for future diabetes. Applicant is advised that if this argument were to be found persuasive then a rejection for lack of enablement would be required given the fact that the example in the specification does not show said predictive value either.

Applicant cites the Example in support.

A careful review of the Example reveals that its methodology is so flawed as to render the results meaningless. Table 1 clearly shows that the majority of the "Cases" in the study did not meet Applicant's definition of "apparently health". Note that 58.5% of the individuals reported a "History of Hypertension". Another 43.6 of the "Cases" reported a "History of Hyperlipidemia". "Apparently healthy" is defined at page 9 as "free of symptoms of disease", which most of the subjects in this study clearly were not.

Applicant argues that Chapin et al. describes asymptomatic individuals whereas the claims are drawn to a method involving apparently healthy individuals.

A review of the specification reveals that apparently healthy individuals is defined as including individuals absent symptoms and previous clinical evidence of disease. Before the tests of Chapin et al. the subjects presented no clinical evidence of disease and, thus, they were included in the study because they were "apparently healthy". Indeed, individuals with known diabetes were excluded from the tests.

The testing of apparently healthy individuals for diseases and conditions which they do not know they have is the hallmark of preventive medicine. Whether it be taking a blood pressure to check for possible hypertension, checking PSA levels to check for the possibility of prostate cancer (including future prostate cancer), or checking genetic polymorphisms as predictor of future cancers, the screening of apparently healthy individuals employing markers found in blood or other tissue for a myriad of future problems is routine and obvious in the medical art.

Applicant's arguments, filed 1/09/09, have been fully considered but are not found persuasive. Applicant again argues that the primary reference, Rodriguez-Moran et al. (1999), did not address whether CRP levels could predict future diabetes.

Clearly, but the skilled artisan would have combined the teachings of all of the references to develop a method for predicting future diabetes as set forth above.

Applicant again argues that Chapin et al. does not teach "apparently healthy" individuals as defined by the specification at page 9.

A review of the specification discloses that "apparently healthy" individuals are defined as not exhibiting symptoms or free of symptoms of disease. As is well-known to the ordinarily skilled medical practitioner, "symptoms" are the subjective evidence of disease as perceived by an individual. See, for

example, Online-Biology.org or emergerncymedicaled.com (both enclosed). Also note that Applicant refers to the subjects of Chapin et al. as "asymptomatic" (page 8 of the instant remarks). Thus, the patients, being asymptomatic, report no symptoms to the physician and, accordingly, the individuals of the reference are "apparently healthy".

Applicant describes the Women's Health Study (WHS) of Buring et al.(1992) arguing that the claimed method is enabled.

While the basis for the claimed invention may be the WHS, the claimed method must be described in, and enabled by, the instant specification. But as no rejection for lack of enablement has been made, the argument is moot. Regardless, the fact remains that the majority of "cases" as set forth in Table 1 report a history of hypertension and/or hyperlipidemia and would thus, likely not be considered to be "apparently healthy".

Applicant's arguments, filed 9/21/09, have been fully considered but are not found persuasive. Applicant has repeated a number of arguments from previous remarks. They will not be addressed again here. Nor will the references, argued again individually, be addressed again individually here given that the rejection is made in view of the teachings of the combined references as well as that which would have been known in the art to the ordinarily skilled artisan at the time of the invention.

Applicant argues that, "the Examiner has also not articulated a rationale nor provided a clear reason why, based on the teachings of the prior art, CRP levels can be used to predict the risk of developing *future* diabetes and diabetes complications in subjects before the diabetes develops". Applicant argues that Rodriguez-Moran et al. teaches that elevated CRP is a result of diabetes and not a cause of disease.

Adequate rationale is set forth in the rejection. CRP was established as a known marker of diabetes. Known disease markers are routinely screened for in "apparently healthy individuals". Also note that the claims do not require that the subject be disease free. An apparently healthy individual might have diabetes and would most certainly also be at risk for developing a diabetic complication. Thus, even if elevated CRP is a result of diabetes and not a cause of disease, an apparently healthy subject with diabetes and elevated CRP would also be at risk for developing a diabetic complication.

Applicant argues that the subjects of Rohfling et al. and Chapin et al. cannot be considered to be apparently healthy.

Applicant is simply incorrect regarding the teachings of Chapin et al., the subjects taught therein are apparently healthy. Regarding the teachings of Rohfling et al. the reference teaches the screening and diagnosis of diabetes. "Screening" in particular is routinely done on apparently healthy individuals rendering it obvious.

Applicant argues that the subjects of the instant study were free of reported diabetes.

It is unclear how Applicant's argument is relevant to the Examiner's statement that the subjects of the instant study were not "apparently healthy" as defined by the instant specification. "Free of reported diabetes" is most certainly not synonymous with "apparently healthy". See the body of the rejection regarding the apparent health of the subjects of the study of the specification, e.g., 58.5% of the individuals reported a "History of Hypertension".

5. Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schalkwijk et al. (1999) in view of Rohlfing et al. (2000) and Chapin et al. (1999).

As set forth previously, Schalkwijk et al. teaches that elevated serum CRP levels have been found in type I diabetics and in diabetics with foot ulcers (see particularly page 211, **Results** and Table 2).

Schalkwijk et al. does not teach the characterizing a risk profile for developing diabetes in an apparently healthy individual nor evaluating the likelihood that an individual will benefit from treatment.

Rohlfing et al. and Chapin et al. have been discussed above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made measure serum CRP levels for uses such as characterizing a risk profile for developing diabetes in an apparently healthy individual or evaluating the likelihood that an individual will benefit from treatment given CRP's known association with type I diabetes, as taught by Schalkwijk et al., given that it is well known to measure a known marker for the presence of, or predisposition to, diabetes, as taught by Rohlfing et al., even in apparently healthy individuals because even apparently health individuals can suffer from undiagnosed diabetes and/or complications thereof, as taught by Chapin et al. Note that the choice of any particular serum CRP concentration as an indicator of disease comprises no more than routine optimization of the claimed method and falls well within the purview of the ordinarily skilled artisan.

Applicant presents arguments essentially the same as presented regarding the rejection in view of Rodriguez-Moran et al., e.g., that the primary reference does not show that elevated CRP is predictive of diabetes.

See the Examiner's response in Section 4. Regarding whether or not elevated CRP is the cause of, or result of, diabetes is irrelevant; as set forth previously, the basis of much of preventive medicine is the finding of markers that show evidence of disease before signs and symptoms occur and C-reactive protein was a well-known marker for diabetes. Also again note that, as set forth above, an apparently healthy individual might have diabetes and would most certainly also be at risk for developing a diabetic complication. Thus, Applicant's continued stressing that the claims recite the predicting of future diabetes is only partially correct.

Also note that Applicant's cite from page 356 of Schalkwijk et al. mainly concerns "glycated end products" with just a single sentence regarding CRP, "Another possibility is that increases in CRP are related to adipose-tissue-derived cytokines." This last sentence is silent regarding the possibility of CRP being present before the onset of diabetes. Thus, the reference does not teach away from the claimed method.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75, and 76 stand rejected under 35 U.S.C. 102(b) as being anticipated by Ford (1999).

As set forth previously, Ford teaches obtaining a level of C-reactive in a blood sample (see particularly Research Design and Methods). As obtaining a level of C-reactive in a blood sample is the only actual step in the claimed method the reference clearly anticipates the method of the claims.

Applicant's arguments, filed 9/21/09, have been fully considered but are not found persuasive. Applicant argues that the reference does not teach "characterizing".

Applicant is advised that in the instant context "characterizing" appears too comprise at most only a mental step that carries no patentable weight. Accordingly the rejection is maintained.

8. Claims 11, 16, 73, and 74 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Rodriguez-Moran et al. (1999) in view of Rohlfing et al. (2000) and Chapin et al. (1999) as applied to Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76 above, and further in view of Dods and Bolmey (1979).

As set forth previously, Rodriguez-Moran et al., Rohlfing et al., and Chapin et al. have been described above.

The teachings of the combined references differ from the claimed method only in that they do not teach an assay further comprising the measurement of glycosylated hemoglobin (HbA).

Dods and Bolmey teach that an assay for HbA is routine in the screening for diabetes given that HbA levels are increased in diabetics (see particularly page 764 and Results). The reference further teaches that diabetes is generally diagnosed using multiple screening methods.

Given the teachings of Dods and Bolmey it would have been obvious to employ the method of Dods and Bolmey in combination with the combined method of Rodriguez-Moran et al., Rohlfing et al., and Chapin et al. to achieve a superior or more accurate prediction of diabetes given that an assay for HbA is routine in the screening for diabetes and that multiple methods of screening are often combined to establish the presence of disease.

Applicant's arguments, filed 9/21/09, have been fully considered but are not found persuasive. Applicant argues that there was a poor correlation between the results of the tests of Dods and Bolmey.

It would seem then that there was even more motivation to combine additional assays/tests to provide more reliable diagnosis of diabetes.

9. Claims 11, 16, 73, and 74 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schalkwijk et al. (1999) in view of Rohlfing et al. (2000) and Chapin et al. (1999) as applied to Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76 above, and further in view of Dods and Bolmey (1979).

As set forth previously, Schalkwijk et al., Rohlfing et al., Chapin et al., and Dods and Bolmey have been described above.

Given the teachings of Dods and Bolmey it would have been obvious to employ the method of Dods and Bolmey in combination with the combined method of Rodriguez-Moran et al., Rohlfing et al., and Chapin et al. to achieve a superior or more accurate prediction of diabetes given that an assay for HbA is routine in the screening for diabetes and that multiple methods of screening are often combined to establish the presence of disease.

Applicant has not addressed this rejection separately. See sections 4-9, above.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically:

As set forth previously, it is unclear whether or not the "characterizing" and "comparing" of the claims are actually steps, or not, and further, precisely what the "characterizing" encompasses. As set forth in MPEP 608.01(m), each step of a claim must be indented. Whereas the characterizing step is indented in Claim 11 (implying that it is an actual step), characterizing is not indented in Claims 1, 21, and 68. The possible "comparing" step of Claim 11 is not indented. Further, as said "characterizing" is not defined in the specification, the metes and bounds of the actual action of the step cannot be determined.

Applicant argues that "characterizing" is, "recognized and discernable to one of ordinary skill…".

It remains the Examiner's position that the term is vague and indefinite as used in the instant claim context. Applicant's mere allegation that it is not is not persuasive.

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on (571) 272-0878.

15. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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